Original Article

Evaluation of rare but severe immune related adverse effects in PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a meta-analysis

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Background: Programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) inhibitor therapy is showing marked efficacy in advanced non-small cell lung cancer (NSCLC). Meanwhile, it is concomitant with distinctive immune-related adverse effects. We aim to describe the incidence of pneumonitis and other rare but severe immune-related adverse effects (IRAEs), as well as treatment related deaths. In addition, we analyze the differences in incidence of pneumonitis between PD-1 and PD-L1 inhibitors and standard-of-care chemotherapy.

Methods: PubMed was searched up to 24 March 2017 for clinical trials of PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) in treatment of NSCLC. Besides, references of relevant articles were screened.

Results: Finally, 22 trials were included in our study, 14 with data of pneumonitis, 19 with other severe IRAEs or treatment related deaths and 5 with control groups. Incidence of all-grade pneumonitis was 2.9% (95% CI, 2.0–4.8%) and grade 3 or higher pneumonitis 2.0% (95% CI, 1.0–2.0%). Incidence of all-grade pneumonitis in PD-1 and PD-L1 inhibitor therapy (n=1,313) was significantly higher than that in chemotherapy (n=918) (OR=2.35, 95% CI, 1.32–4.20, P=0.004), but had no significance in grade 3–5 pneumonitis. Incidence of cardiorespiratory arrest (n=537) was 1.0% (95% CI, 0–2.0%), cardiac failure (n=214) 2.0% (95% CI, 1.0–5.7%), myocardial infarction (n=402) 1.0% (95% CI, 0–3.8%), stroke (n=135) 2.0% (95% CI, 0–13.0%), disease progression (n=391) 1.0% (95% CI, 0–2.9%), pancreatitis (n=700) 1.0% (95% CI, 0–2.0%) and severe skin reactions (n=836) 2.0% (95% CI, 1.0–3.8%). Incidence of treatment related deaths was 0.7%.

Conclusions: Immune related adverse effects can on occasion be life-threatening even though usually rare. Incidence of pneumonitis in PD-1 and PD-L1 inhibitors was significantly higher than that in chemotherapy. More studies should be conducted to investigate the incidence of these rare but life-threatening IRAEs.

Keywords: Adverse drug events; immunotherapies; pneumonitis; programmed cell death 1 protein; programmed cell death 1 ligand 1

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Introduction

Programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) inhibitors are thriving in anti-cancer treatment. PD-1 was expressed by activated T lymphocytes. It combines with its ligands PD-L1 to restrict the activation of T lymphocytes and prevent autoimmune disease. Monoclonal antibodies targeting PD-1 and PD-L1 can block the immune checkpoint and eliminate the inhibition of T lymphocytes activation. As a result, they largely enhance immune reactions to fight against malignant tumors (1,2). Several PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) are showing distinct activities and efficacy in treatment of advanced melanoma, renal cell carcinoma and non-small cell lung cancer (NSCLC) or Hodgkin lymphoma.

However, for its character of blocking inhibitory regulation and leading to unregulated activation of immune reaction, when the potency of fighting against cancer increased significantly, it may also affect other organs and injure normal tissues, which consequently lead to immune-related adverse effects (IRAEs) (3). A wide range of organs and systems may be involved, and skin, gastrointestinal tract and liver are the most commonly affected. Preclinical researches, animal experiments and pathological specimens of clinical patients found abundant infiltration of activated T CD8 positive lymphocytes in involved organs. Usually, IRAEs of checkpoint inhibitors are mild and could be managed by clinicians. However, some serious adverse effects must be controlled by discontinuation of drugs, temporarily or even permanently. Pneumonitis is one of the IRAEs that reported by most clinical trials, and severe cases may lead to death. Besides, some rare toxic effects affecting cardiovascular and respiratory systems should raise our concern because they may be deadly once occur and possibly unrecognized as immune-related adverse effects. Incidence of pneumonitis in PD-1 and PD-L1 inhibitor therapy has been reported in several metanalysis, as well as differences in incidence between NSCLC and melanoma, and PD-1 and PD-L1 inhibitors (4,5). However, no metanalysis explored the incidence of these rare but life-threatening IRAEs, such as immune related myocarditis.

The objective of this study was to investigate the incidence of pneumonitis and other rare but life-threatening adverse effects, as well as treatment related deaths in PD-1 and PD-L1 inhibitor therapy for treatment of NSCLC. Meanwhile, we compare differences in incidence of pneumonitis between PD-1 and PD-L1 inhibitor therapy and standard-of-care chemotherapy.

Methods

Search methods and study selection

Clinical trials of PD-1 and PD-L1 inhibitors for treatment of lung neoplasms were searched through PubMed, using the key words of PD-1 and PD-L1 monoclonal antibody, nivolumab, pembrolizumab, atezolizumab, avelumab and durvalumab. Besides, references of relevant articles were searched for meeting abstracts and possible omission. Articles meeting the following criteria were included: (I) phases I–III clinical trials; (II) measure the safety profile of PD-1 and PD-L1 inhibitors; (III) single-arm trials of PD-1 and PD-L1 inhibitors or PD-1 and PD-L1 inhibitors versus chemotherapy. Trials of combined therapy of cytotoxic T lymphocyte associated antigen 4 (CTLA-4) inhibitors and PD-1 and PD-L1 inhibitors were excluded for that they would increase the incidence of pneumonitis and we may fail to distinguish the adverse effects of which drug. When results of the same clinical trial were reported at different time, only the most recent, or the most complete report was included. All the articles were screened independently by two authors (YB Hu and Q Zhang).

Data extraction

Data including clinical trial information of the study, first author, year of publication, trial phases, study drugs, total number of patients evaluated for safety, number of

patients with pneumonitis, other rare but life-threatening adverse effects including cardiac failure, cardiorespiratory arrest, myocardial infarction, stroke, disease progression, pancreatitis, severe skin reactions, sepsis, pulmonary embolism, respiratory arrest, respiratory failure, constrictive pericarditis, cardiac tamponade, pericardial effusion, encephalitis, myocarditis, sarcoidosis, endophthalmitis, and myasthenia gravis, as well as treatment related deaths were extracted. Infectious related pneumonia was not included. Because phase I trials were commonly dose escalation, the number of an adverse event which developed from the study drug were counted together, regardless of doses. Any data not reported in the primary articles were represented as "not applicable". We didn't contact the author for detailed information. The main outcomes were incidence of pneumonitis and other rare but life-threatening adverse effects in PD-1 and PD-L1 inhibitor therapy, cases of treatment related deaths, and differences in incidence of pneumonitis between checkpoint inhibitor therapy and chemotherapy.

Statistical analysis

Review manager version 5.3 was used for statistical analysis. For trials with control groups, data type of dichotomous was selected to compare the incidence of pneumonitis between PD-1 and PD-L1 inhibitor therapy and standard-of-care chemotherapy. For single arm trials, data type of generic inverse variance was selected.

For the outcome of incidence, if P value was not close to 0 or 1 and both n*P and n*(1–P) were more than 5, P could be calculated by n/X [1], in which n and X referred to the number of patients with pneumonitis and total number of patients evaluated for safety, respectively. Standard error (SE) could be calculated using the formula of $(P(1–P)/n)^{1/2}$ [2], in which P and n had the same meaning with above. On the other hand, if the above condition could not be met, P and SE must be calculated by the below formulas: P= ln(odds) = ln[X/(n–X)] [3], SE(P) = SE[ln(odds)] = $[1/X+1/(n–X)]^{1/2}$[4]. Significantly, this is the method used for categorical data, thus the calculations OR should be transformed using the following formula: Pf = OR/(1+ OR) [5], lower limit (LL) of 95% confidence interval (CI) = $LL_{OR}/(1+ LL_{OR})$ [6], upper limit (UL) = $UL_{OR}/(1+ UL_{OR})$ [7]. Due to the low incidence of adverse effects in our study, the latter method was adopted.

Heterogeneity was evaluated by Cochran chi-square test and the I^2 test. Heterogeneity was thought to be exist if P value was less than 0.05. If the homogeneity of ORs were fine (P>0.05), a fixed effect model was used; if not (P<0.05), a random effect model was used. I^2<30% represented a slight level of heterogeneity, 30–60% was moderate while I^2>60% meant the heterogeneity was high. Chi-square test was performed for rate differences between two or more categorical data by SPSS version 20.0.

Results

Eligible studies and characteristics

Totally, 1,956 publications were searched on PubMed up to 24 March 2017 and 61 abstracts were identified from reference lists of relevant articles. A total of 1,554 texts were screened after duplications removed, and 1,526 were excluded for reasons of not clinical trials, not of PD-1 and PD-L1 inhibitor therapy, not for treatment of NSCLC, and no information of adverse effects. Consequently, 28 articles were assessed for eligibility, and six were excluded, with one had no numerical data of adverse effects, one of combined therapy of CTLA-4 and PD-L1 inhibitor, and the left four had no data of pneumonitis and other needed information. Finally, 22 trials were included (6-27), 14 with data of pneumonitis were included for meta-analysis (6-10,12-18,20,21) (*Figure 1*). Five had control groups, with two of nivolumab *vs.* docetaxel (13,14), one of pembrolizumab *vs.* docetaxel (16), one of pembrolizumab *vs.* chemotherapy (pemetrexed plus carboplatin) (15) and one of pembrolizumab plus chemotherapy *vs.* chemotherapy (11). Nineteen reported other rare but life-threatening IRAEs and data of treatment related deaths (6-13,15-17,19,20,22-27).

Tables 1,2 are summary of the characteristics of all the included trials. Among them, 11 were phase I trials, 6 were phase II, 3 phase III, 1 phase II/III and the last one was phase IIIB/IV trial; 17 were PD-1 inhibitors (10 nivolumab and 7 pembrolizumab), and 5 were PD-L1 inhibitors (4 atezolizumab and 1 avelumab).

Incidence of pneumonitis

Incidence of all-grade pneumonitis (n=3,542) was 2.9% (95% CI, 2.0–4.8%, P=0.0003, I^2=66%) (*Figure 2A*), and it was 2.0% (95% CI, 1.0–2.0%, P=0.30, I^2=14%) of grade 3–5 pneumonitis (*Figure 2B*). Considering of the high heterogeneity, incidence of pneumonitis in full texts and abstracts were analyzed respectively. Results revealed that

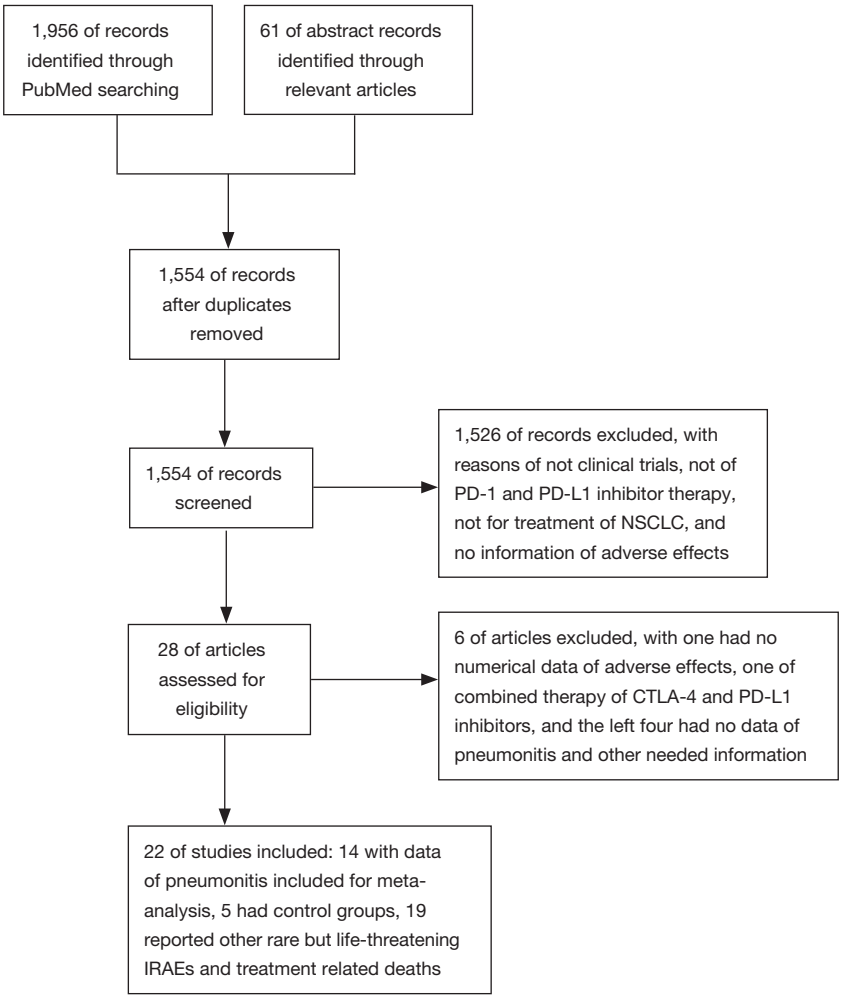

Figure 1 Flow diagram of study selection. NSCLC, non-small cell lung cancer.

incidence of pneumonitis was 4.8% (95% CI, 3.8–5.7%, P=0.13, I^2=34%) of all-grade (*Figure 2C*) and 2.0% (95% CI, 2.0–2.9%, P=0.64, I^2=0) of grade 3–5 (*Figure 2D*) in published full texts (n=2,361). On the other hand, it was 1.0% (95% CI, 1.0–2.0%, P=0.66, I^2=0) of all-grade (*Figure 2E*) and 1.0% (95% CI, 0–2.0%, P=0.63, I^2=0) (*Figure 2F*) in reported abstracts (n=1,181).

Incidence of pneumonitis in PD-1 and PD-L1 inhibitor therapy vs. standard-of-care chemotherapy

In the five trials with control groups, incidence of any grade pneumonitis in PD-1 and PD-L1 inhibitor therapy (n=1,313) was significantly higher than that in chemotherapy (n=918) (OR=2.35, 95%CI, 1.32–4.20, P=0.004) **(***Figure 3A***)**. However, in the case of grade 3–5 pneumonitis, it was higher in PD-1 and PD-L1 inhibitor therapy, but was not statistically significant (P=0.24) (*Figure 3B*).

Incidence of other rare but life-threatening adverse effects

Incidence of some other rare adverse effects were 1.0% (95% CI, 0–2.0%) of cardiorespiratory arrest (n=537) *(Figure 4A*), 2.0% (95% CI, 1.0–5.7%) of cardiac failure (n=214) (*Figure 4B*), 1.0% (95% CI, 0–3.8%) of myocardial infarction (n=402) (*Figure 4C*), 2.0% (95% CI, 0–13.0%) of stroke (n=135) (*Figure 4D*), 1.0% (95% CI, 0–2.9%) of disease progression (n=391) (*Figure 4E*), 1.0% (95% CI, 0–2.0%) of pancreatitis (n=700) (*Figure 4F*) and 2.0% (95% CI, 1.0–3.8%) of severe skin reactions (n=836) (*Figure 4G*).

Two cases of sepsis were reported and one of them led

Table1 Characteristics of all included studies

Clinical trial information	First author	Year	Phase	Study drug	PD-1/PD-L1	Study type	Control group	Dose of study drug	Population
NCT02066636	Bauer	2015	IIIB/IV	Nivolumab	PD-1	Single arm	–	3 mg/kg q2w	Advanced NSCLC after failure
NCT02031458	Besse	2015	II	Atezolizumab	PD-L1	Single arm	–	1,200 mg q3w	1L or 2L/3L+ in PD-L1 selected advanced NSCLC
NCT01673867	Borghaei	2015	III	Nivolumab	PD-1	RCT	Docetaxel	3 mg/kg q2w	Advanced NSQ NSCLC after failure
–	Brahmer	2012	I	Nivolumab	PD-1	Single arm	–	1, 3, 10 mg/kg q2w	Advanced NSCLC after failure
NCT00729664	Brahmer	2012	I	Nivolumab	PD-1	Single arm	–	0.3, 1, 3, 10 mg/kg q2w	Advanced NSCLC after failure
NCT01642004	Brahmer	2015	III	Nivolumab	PD-1	RCT	Docetaxel	3 mg/kg q2w	Advanced SQ NSCLC after failure
NCT01903993	Ferenbacher	2016	II	Atezolizumab	PD-L1	Single arm	–	1,200 mg q3w	Advanced NSCLC after failure
NCT01295827	Garon	2014	I	Pembrolizumab	PD-1	Single arm	–	10 mg/kg q2,3w	Advanced NSCLC after failure
NCT01295827	Garon	2015	I	Pembrolizumab	PD-1	Single arm	–	2, 10 mg/kg q3w; 10 mg/kg q2w	Advanced NSCLC
NCT00730639	Gettinger	2015	I	Nivolumab	PD-1	Single arm	–	1, 3, 10 mg/kg, q2w	Advanced NSCLC after failure
NCT01454102	Gettinger	2016	I	Nivolumab	PD-1	Single arm	–	3 mg/kg q2w	Chemotherapy-naïve advanced NSCLC
NCT02085070	Goldberg	2016	II	Pembrolizumab	PD-1	Single arm	–	10 mg/kg q2w	Advanced NSCLC with untreated brain metastasis
NCT01772004	Gulley	2015	IB	Avelumab	PD-L1	Single arm	–	10 mg/kg q2w	Advanced NSCLC after failure
NCT01905657	Herbst	2016	II/III	Pembrolizumab	PD-1	RCT	Docetaxel	2, 10 mg/kg q3w	NSCLC after failure
NCT01375824	Horn	2015	IA	Atezolizumab	PD-L1	Single arm	–	≤20 mg/kg q3w	NSCLC
NCT02039674	Langer	2016	II	Pembrolizumab	PD-1	RCT	Pemetrexed + carboplatin	200 mg	Chemotherapy-naïve NSQ NSCLC
NCT02142738	Reck	2016	III	Pembrolizumab	PD-1	RCT	Chemotherapy	200 mg q3w,	Treatment-naïve
–	Rizvi	2014	I	Nivolumab	PD-1	Single arm	–	3 mg/kg q2w	Chemotherapy-naïve NSCLC

Table 1 *(continued)*

Table 1 *(continued)*

Clinical trial information	First author	Year	Phase	Study drug	PD-1/PD-L1	Study type	Control group	Dose of study drug	Population
NCT01721759	Rizvi	2015	II	Nivolumab	PD-1	Single arm	–	3 mg/kg q2w	Advanced SQ NSCLC after failure
NCT01295827	Soria	2015	I	Pembrolizumab	PD-1	Single arm	–	2, 10 mg/kg q3w; 10 mg/kg q2w	Advanced NSCLC after failure
NCT01846416	Spigel	2015	II	Atezolizumab	PD-L1	Single arm	–	1,200 mg q3w	Advanced NSCLC after failure
NCT00730639	Topalian	2012	I	Nivolumab	PD-1	Single arm	–	1, 3, 10 mg/kg, q2w	Advanced NSCLC after failure

PD-1, programmed death-1; PD-L1, programmed death ligand-1; NSCLC, non-small cell lung cancer; RCT, randomized control trial; q2w, every two weeks; q3w, every three weeks; NSQ, non-squamous cell; SQ NSCLC, squamous cell NSCLC.

to death (n=59). Cases of pulmonary embolism, respiratory arrest, respiratory failure, constrictive pericarditis, cardiac tamponade, pericardial effusion, encephalitis, myocarditis, sarcoidosis, endophthalmitis and myasthenia gravis were reported each by one case. Three cases of respiratory arrest, respiratory failure and constrictive pericarditis had led to deaths of patients (treated with pembrolizumab, avelumab and atezolizumab respectively). All the other cases were treated with nivolumab. What's more, except for myocarditis of grades 1–2, all the others were grades 3–4 in severity (*Table 3*).

Treatment related deaths

Totally, 29 deaths related to treatment were reported (n=4,160). There was no significant difference between the rate of death in PD-1 and PD-L1 inhibitors (P=0.626). Four deaths were attribute to pneumonitis, four pneumonias and another one radiation pneumonitis. Other causes leading to deaths included cardiac failure, respiratory failure, respiratory arrest, constrictive pericarditis, encephalitis, ischemic stroke, myocardial infarction, sepsis (each n=1), and interstitial lung disease (ILD) and cardiorespiratory arrest (each n=2), as well as disease progression (n=3) and unknown causes (n=5) (*Table 4*).

Discussion

This metanalysis revealed in patients with lung cancer treated with PD-1 and PD-L1 inhibitors the overall incidence of pneumonitis was 2.9% for all-grade and 2.0% for grade 3–5. Nishino et.al summarized in NSCLC treated with PD-1 inhibitor monotherapy the incidence of pneumonitis was 4.1% for all-grade and 1.8% for grade 3–5, both of which were significantly higher than that in melanoma (4). Besides, Khunger *et al.* found incidence of all-grade pneumonitis is 3.6% in PD-1 inhibitors and 1.3% in PD-L1 inhibitors, while it was 1.1% and 0.4% of grade 3–5 pneumonitis (5). Cardiovascular toxicities associated with immune checkpoint inhibitors have been serially reported mainly related to CTLA-4 inhibitors or combined therapy with PD-1 and PD-L1 antibodies, such as myocarditis, heart failure, cardiomyopathy, myocardial fibrosis, cardiac arrest, and complete heart block (28-31). Information of cardiac side effects of anti-PD-1 and anti-PD-L1 on patients with lung cancer were limited. Laubli *et al.* reported a case of heart failure due to autoimmune myocarditis after treating melanoma with pembrolizumab. Cardiac biopsy showed

Table2 Characteristics of all included studies

Clinical trial information	Total number of patients	Number of any grade pneumonitis	Number of grades 3–5 pneumonitis	Total in control group	Number of any grade pneumonitis in control	Number of grades 3–5 pneumonitis in control
NCT02066636	226	3	1	–	–	–
NCT02031458	659	4	4	–	–	–
NCT01673867	287	4	3	268	0	0
–	75	1	1	–	–	–
NCT00729664	207	–	–	–	–	–
NCT01642004	131	6	0	129	0	0
NCT01903993	142	–	–	–	–	–
NCT01295827	221	3	3	–	–	–
NCT01295827	495	18	9	–	–	–
NCT00730639	129	11	4	–	–	–
NCT01454102	52	3	1	–	–	–
NCT02085070	18	1	1	–	–	–
NCT01772004	184	–	–	–	–	–
NCT01905657	682	31	14	309	4	0
NCT01375824	88	–	–	–	–	–
NCT02039674	59	–	–	62	–	–
NCT02142738	154	9	4	150	1	1
–	20	–	–	–	–	–
NCT01721759	117	6	4	–	–	–
NCT01295827	449	–	–	–	–	–
NCT01846416	137	–	–	–	–	–
NCT00730639	296	9	3	–	–	–

infiltration of CD8 positive T lymphocytes and a reduction of FOXP3 positive regulatory T cells (32). Semper *et al.* made known a patient with lung squamous cell carcinoma developed myocarditis after treatment of nivolumab (33); and Behling *et al.* gave an account of a case of myositis with treatment of nivolumab for metastatic melanoma, which then developed to third-degree atrioventricular block (34). Despite of the low incidence, they should be brought to the forefront. Any symptoms and signs should give rise to rapid and comprehensive cardiovascular evaluation, and prompt and effective therapeutic approaches are dictated, such as respiratory and hemodynamic support, even heart transplant if necessary.

Clinical trials demonstrated treatment-related adverse effects in PD-1 and PD-L1 inhibitors were fewer than that in docetaxel or chemotherapy (13-15). However, we proved patients treated with PD-1 and PD-L1 inhibitors had higher incidence of pneumonitis than chemotherapy. Nishijima *et al.* compared the safety and tolerability of PD-1 and PD-L1 inhibitors with chemotherapy and demonstrated incidence of any adverse effects of checkpoint inhibitors were significantly lower than chemotherapy, both all-grade and high grade, as well as the frequency of discontinued treatment for toxicity. However, PD-1 and PD-L1 inhibitors were associated with higher risk of all-grade rash, colitis, hypothyroidism, hyperthyroidism, and aminotransferase elevations, and all- and high-grade pneumonitis (35).

IRAEs were normal mild and could be managed by clinicians. However, some severe cases may be deadly and lead to deaths without effective measures could be taken. Thus, prevention, early recognition and prompt intervention are of great importance in management of these severe cases. Firstly, clinicians should evaluate the base-line status of patients and recognize possible risk factors that may contribute to the development of

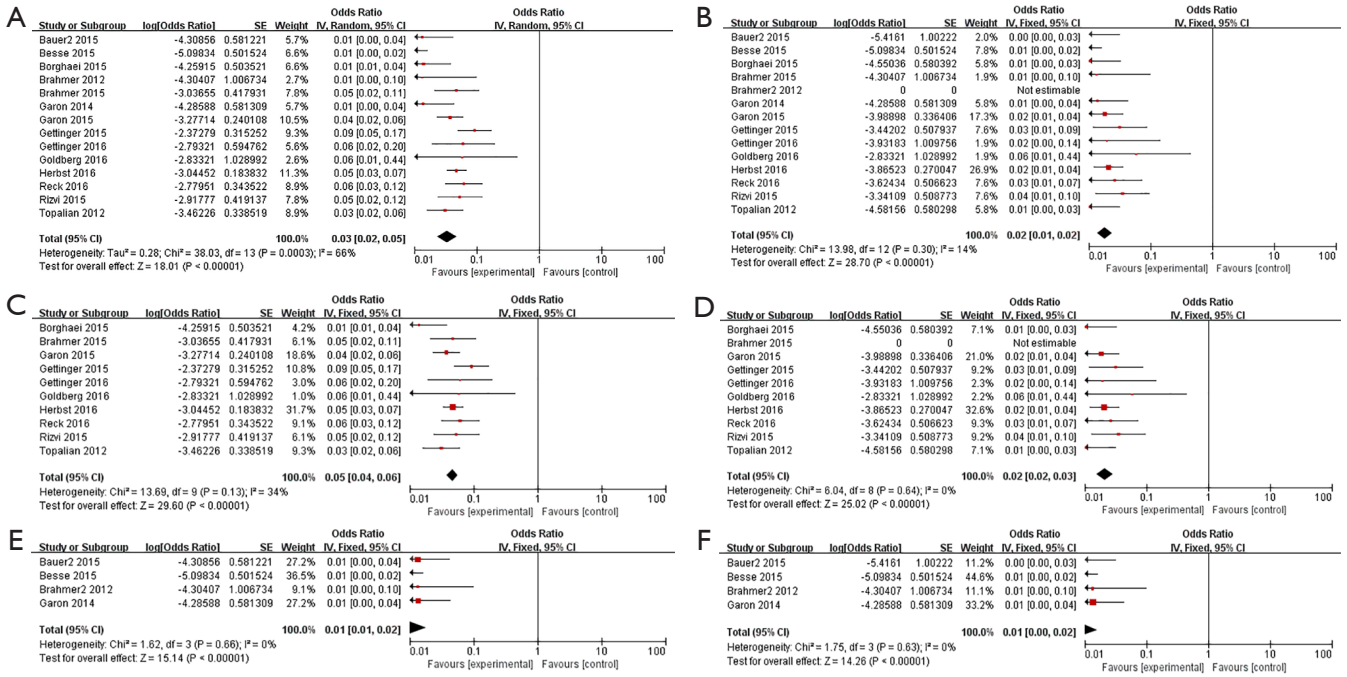

Figure 2 Forest plots of incidence of pneumonitis. (A) Incidence of all-grade pneumonitis; (B) incidence of grades 3–5 pneumonitis; (C) incidence of all-grade pneumonitis in published full-texts; (D) incidence of grades 3–5 pneumonitis in published full-texts; (E) incidence of all-grade pneumonitis in reported abstracts; (F) incidence of grades 3–5 pneumonitis in reported abstracts.

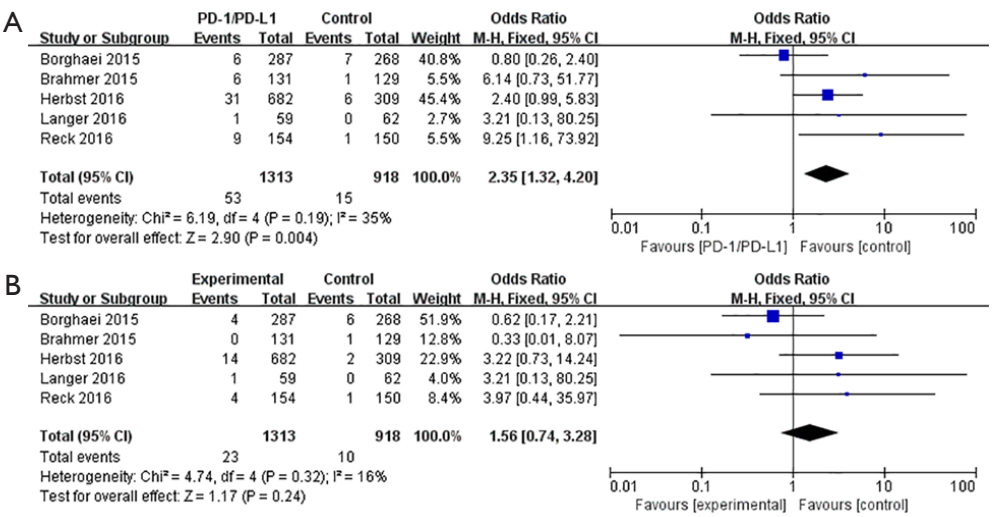

Figure 3 Forest plots of differences in incidence of pneumonitis between PD-1 and PD-L1 inhibitors and chemotherapy. (A) Difference in incidence of all-grade pneumonitis between PD-1 and PD-L1 inhibitors and chemotherapy; (B) difference in incidence of grades 3–5 pneumonitis between PD-1 and PD-L1 inhibitors and chemotherapy. PD-1, programmed death-1; PD-L1, programmed death ligand-1

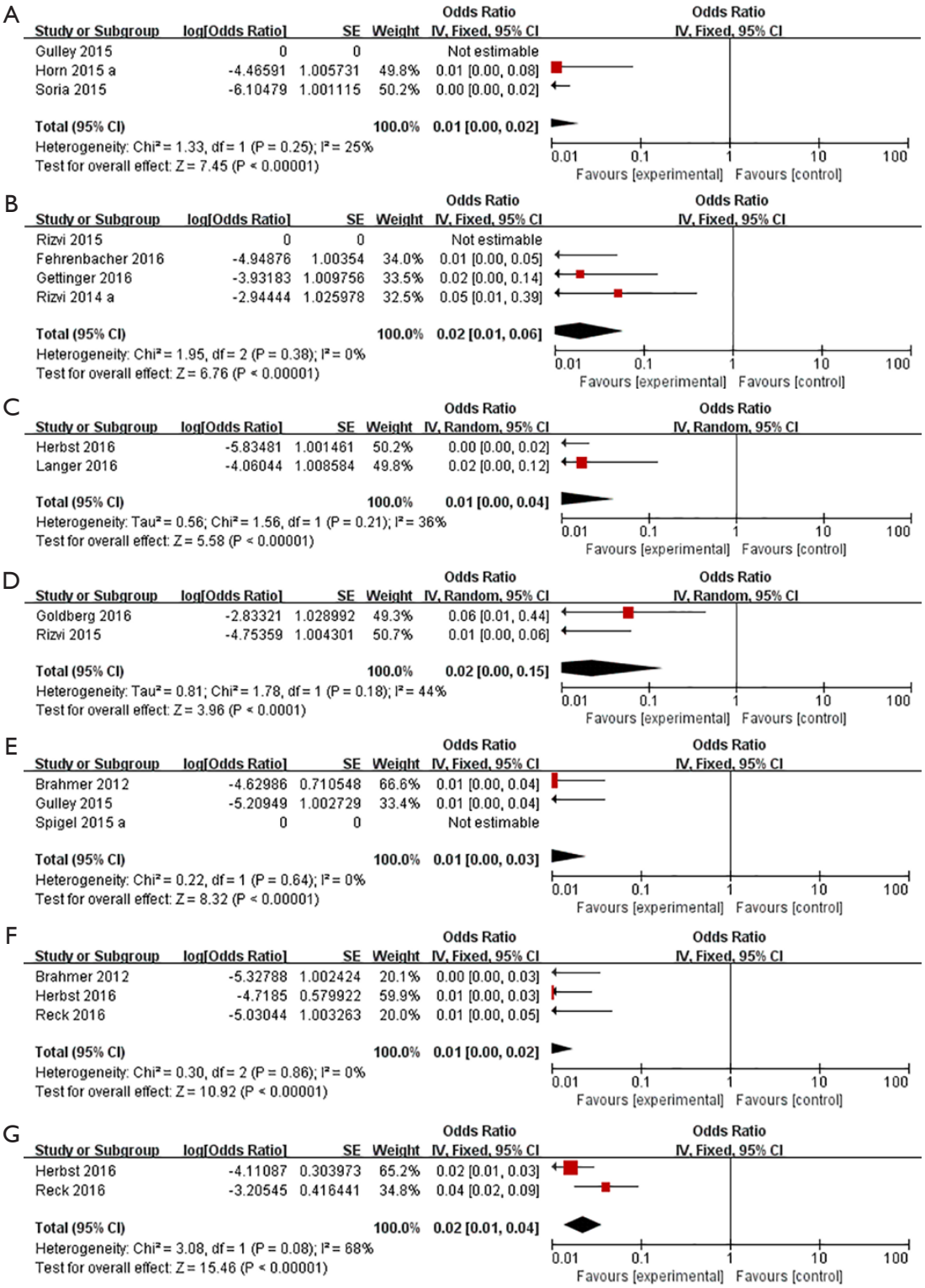

Figure 4 Forest plots of incidence of some rare but severe adverse effects. (A) Cardiorespiratory arrest; (B) cardiac failure; (C) myocardial infarction; (D) stroke; (E) disease progression; (F) pancreatitis; (G) severe skin reactions.

Table 3 Incidence of other rare but life-threatening IRAEs

Adverse effects	First author	Year of publication	Study drugs	Total number of patients	Events
Cardiac failure	Gettinger	2016	Nivolumab	52	1
	Rizvi	2014	Nivolumab	20	1
	Fehrenbacher	2016	Atezolizumab	142	1
Cardiorespiratory arrest	Horn	2015	Atezolizumab	88	1
	Soria	2015	Pembrolizumab	449	1
Myocardial infarction	Langer	2016	Pembrolizumab	59	1
	Herbst	2016	Pembrolizumab	343	1
Stroke	Goldberg	2016	Pembrolizumab	18	1
	Rizvi	2015	Nivolumab	117	1
Disease progression	Gulley	2015	Avelumab	184	1
	Brahmer	2012	Nivolumab	207	2
Pancreatitis	Brahmer	2012	Nivolumab	207	1
	Herbst	2016	Pembrolizumab	339	3
	Reck	2016	Pembrolizumab	154	1
Severe skin reactions	Herbst	2016	Pembrolizumab	682	11
	Reck	2016	Pembrolizumab	154	6
Sepsis	Langer	2016	Pembrolizumab	59	2
Pulmonary embolism	Borghaei	2015	Nivolumab	287	1
Respiratory arrest	Soria	2015	Pembrolizumab	449	1
Respiratory failure	Gulley	2015	Avelumab	184	1
Constrictive pericarditis	Spigel	2015	Atezolizumab	137	1
Cardiac tamponade	Borghaei	2015	Nivolumab	287	1
Pericardial effusion	Borghaei	2015	Nivolumab	287	1
Encephalitis	Borghaei	2015	Nivolumab	287	1
Myocarditis	Brahmer	2012	Nivolumab	207	1
Sarcoidosis	Brahmer	2012	Nivolumab	207	1
Endophthalmitis	Brahmer	2012	Nivolumab	207	1
Myasthenia gravis	Brahmer	2012	Nivolumab	207	1

IRAEs, immune-related adverse effects.

treatment-related adverse effects. Besides, patients and their family members should be educated to identify early symptoms so that prompt intervention could be taken. Meanwhile, during the course of treatment, regular examinations and closely monitor of patients were vital. Nevertheless, if IRAEs already developed, measures should be taken to control them without delay. For grades 1–2 AEs, discontinuation of therapeutic drugs may not be necessary. However, for grades 3–4 AEs, discontinuation of drugs is necessary, temporarily or even permanent. Besides, corticosteroid may be needed from time to time and it must be used rationally.

As well described by Naidoo, patients exposed to corticosteroids for IRAE become immunocompromised, as

Table 4 Trials reporting treatment-related deaths and causes of deaths

First author	Year	Study drug	PD-1/PD-L1	Events	Total number of patients	Causes of deaths
Besse	2015	Atezolizumab	PD-L1	1	659	Pneumonia
Fehrenbacher	2016	Atezolizumab	PD-L1	1	142	Cardiac failure
Gulley	2015	Avelumab	PD-L1	3	184	Radiation pneumonitis, acute respiratory failure, disease progression
Horn	2015	Atezolizumab	PD-L1	1	88	Cardiorespiratory arrest
Spigel	2015	Atezolizumab	PD-L1	1	137	Constrictive pericarditis
Borghaei	2015	Nivolumab	PD-1	1	287	Encephalitis
Brahmer	2012	Nivolumab	PD-1	1	75	Pulmonary toxicity
Brahmer	2012	Nivolumab	PD-1	2	207	Disease progression
Gettinger	2015	Nivolumab	PD-1	1	129	Pneumonitis
Rizvi	2015	Nivolumab	PD-1	2	117	Pneumonia, ischemic stroke
Soria	2015	Pembrolizumab	PD-1	3	449	Cardiorespiratory arrest, ILD, respiratory arrest
Topalian	2012	Nivolumab	PD-1	3	296	Study drug toxicity
Garon	2015	Pembrolizumab	PD-1	1	495	Interstitial lung disease
Herbst	2016	Pembrolizumab	PD-1	6	682	2 mg/kg (pneumonitis, pneumonia), 10 mg/kg (myocardial infarction, pneumonitis, pneumonia)
Langer	2016	Pembrolizumab	PD-1	1	59	Sepsis
Reck	2016	Pembrolizumab	PD-1	1	154	Unknown cause

PD-1, programmed death-1; PD-L1, programmed death ligand-1; ILD, interstitial lung disease.

a consequence in cases of recurrence of respiratory event it become crucial to carefully ruled out some bacterial or fungal infections such as aspergillosis (36).

Finally, we found in the present metanalysis progression of disease as a side effect of treatment with an incidence of 1.0% (95% CI, 0–2.9%). Recently, Champiat *et al.* reported tumor hyperprogression related to anti-PD1 or anti-PDL1 treatments, defined as a doubling of the tumor growth rate. We believe that a homogenization of the term "hyperprogressive disease" is to be considered in future studies to compare this deleterious and rare side effect across studies (37).

There were some limitations in our study. Firstly, most included trials were open-label, which may lead to selection bias of patients. In addition, data in some abstracts were ambiguous and were not the final results. Moreover, patients included were those highly selective in clinical trials and may not reflect the condition in real world.

Conclusions

Immune related adverse effects can on occasion be life-threatening even though usually rare. This metanalysis demonstrated that incidence of pneumonitis in NSCLC treated with PD-1 and PD-L1 inhibitor therapy was significantly higher than that with chemotherapy. Further metanalysis should be conducted to deeply investigate the incidence of other rare and potentially unrecognized life-threatening IRAEs.

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Footnote

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